

Scientific Abstract

Proposed Clinical Trial: Transduction of the Upper and Lower Airway Epithelium in Healthy Subjects by an AAV2 Vector that Encodes Human Placental Alkaline Phosphatase

The overall objective of this study is to measure transduction rates and immune responses to an AAV2-based vector delivered to the nasal or bronchial epithelium of healthy humans. An AAV2-based vector that encodes human placental alkaline phosphatase (AP) will be used for this study because of the availability of a simple and robust histochemical assay for AP expression, as a measure of vector transduction, and the fact that AP is a normal human protein and should not elicit immune responses against alkaline phosphatase, unlike other markers of transduction derived from other organisms.

The rationale for this study is based on the finding that attempts to treat cystic fibrosis (CF) by delivery of an AAV2-based vector that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) to the airway of patients has not resulted in clinical improvement. In addition, outcome measures for determining efficacy in the treatment of CF are unreliable if the effects of the vector are real but not dramatic. Moreover, it has been technically difficult to detect CFTR expression following vector administration, raising fundamental questions about the adequacy of the AAV2 vector system for gene transfer to airway. We believe that a marker gene transduction study is the best way to evaluate the suitability of AAV vectors for airway transduction. In addition, we have found that other AAV vector types, in particular AAV6, mediate much higher transduction in mouse airway than do AAV2-based vectors, the only AAV vectors to be tested in humans to date, and we plan additional studies to address the question of which AAV vector types work best in humans. We believe that this is the most efficient method to determine the optimal vector for treatment of patients with CF.